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Regulation of amyloid-β production by the prion protein

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Alzheimer disease (AD) is characterized by the amyloidogenic processing of the amyloid precursor protein (APP), culminating in the accumulation of amyloid-β peptides in the brain. The enzymatic action of the β-secretase, BACE1 is the rate-limiting step in this amyloidogenic processing of APP. BACE1 cleavage of wild-type APP (APP_{WT}) is inhibited by the cellular prion protein (PrP^C). Our recent study has revealed the molecular and cellular mechanisms behind this observation by showing that PrP^C directly interacts with the pro-domain of BACE1 in the trans-Golgi network (TGN), decreasing the amount of BACE1 at the cell surface and in endosomes where it cleaves APP_{WT}, while increasing BACE1 in the TGN where it preferentially cleaves APP with the Swedish mutation (APP_{Swe}). PrP^C deletion in transgenic mice expressing the Swedish and Indiana familial mutations ($APP_{Swe,Ind}$) failed to affect amyloid-β accumulation, which is explained by the differential subcellular sites of action of BACE1 toward APP_{WT} and APP_{Swe}. This, together with our observation that PrP^C is reduced in sporadic but not familial AD brain, suggests that PrP^C plays a key protective role against sporadic AD. It also highlights the need for an APP_{WT} transgenic mouse model to understand the molecular and cellular mechanisms underlying sporadic AD.

Keywords: Alzheimer disease, amyloid-β (Aβ), amyloid precursor protein (APP), β-site APP-cleaving enzyme-1 (BACE1), cellular prion protein (PrP^C)

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Alzheimer disease (AD) is the most prevalent form of dementia and currently affects more than 37 million people worldwide.[1,2] Less than 1% of AD cases are known to be caused by inheritable mutations in genes encoding the amyloid precursor protein (APP), presenilin-1 (PS1) and PS2.[3] However, for the majority of AD cases, which are termed sporadic or late-onset, the cause and/or causes remain elusive, although aging is known to be the greatest risk factor.[4] AD is characterized by the accumulation in the brain of the amyloid-β (Aβ) peptide in the form of oligomers and/or fibrils. This peptide is formed by the sequential processing of APP by the β-site APP cleaving enzyme-1 (BACE1) and the PS1 or PS2 containing γ-secretase complex.[5] Depending on the γ-secretase cleavage site, Aβ is released as a 40 or 42 amino acid peptide, with Aβ42 exhibiting a greater propensity for aggregation.[6] In the normal brain, Aβ production and degradation is tightly regulated, but in the AD brain, Aβ homeostasis is altered with elevated levels of Aβ42 and/or an increased ratio of Aβ42:Aβ40.[7] BACE1 is the rate-limiting enzyme in Aβ production and its activity is raised in the brains of sporadic AD patients,[8,9] therefore, understanding how this enzyme is regulated is vitally important and has become a pivotal part of AD research.

The normal cellular form of the prion protein (PrP^C) converts by misfolding into the infectious form, PrP^{Sc}, which is the causative agent in the neurodegenerative transmissible spongiform encephalopathies (TSEs) including Creutzfeldt-Jacob disease (CJD).[10] There are a number of similarities between AD and prion diseases, including the coexistence of AD pathology in some cases of CJD.[11] In addition, PrP^C has been shown to co-localize with Aβ in plaques,[12] which are present in the majority of CJD patients with associated AD-type pathology.[13] A systematic meta-analysis of AD genetic association studies revealed that the gene *PRNP*, which encodes PrP^C, is a potential

AD susceptibility gene[14] and the Met/Val polymorphism at residue 129 in PrP^C has been reported to be a risk factor for early onset AD.[13,15,16] In 2007, we discovered that PrP^C plays a critical role in regulating the activity of BACE1 toward the processing of wild-type APP (APP_{WT}),[17] and proposed that a normal function of PrP^C may be to protect against AD.[18] In addition to PrP^C, various other proteins have been shown to alter the amyloidogenic processing of APP by the modulation of BACE1 activity, including the sorting protein-related receptor (SorLA/LR11),[19,20] ADP ribosylation factor 6 (ARF6),[21] and Golgi-localized γ-ear containing ARF binding proteins (GGAs),[22,23] among others. All of these proteins modulate BACE1 activity by altering the trafficking and localization of BACE1 in relation to APP, as a means to regulate Aβ levels.

In our recent study in reference 24, we extended our work on the role of PrP^C in regulating BACE1 activity by examining the molecular and cellular mechanisms involved. We found that PrP^C forms immuno-complexes with BACE1 in both mice and non-demented human brain samples. The interaction between BACE1 and PrP^C was investigated using recombinant proteins by enzyme linked immunosorbent assay (ELISA) and surface plasmon resonance (SPR) to reveal a direct interaction between PrP^C and the pro-domain of BACE1. As PrP^C also inhibited the BACE2 mediated processing of APP, we identified a conserved sequence (LPLR) in the pro-domains of both proteins which we interrogated in BACE1 by site-directed mutagenesis. The L28Q/L30Q mutant did not traffic properly through the secretory pathway and was only present in its immature ER form, indicating that these residues are particularly important for the trafficking of BACE1. In contrast the P29G mutation resulted in comparable maturation and activity to wild-type BACE1, but the inhibitory effect of PrP^C on BACE1 activity was lost, indicating that Pro29 is critical for the protein-protein interaction.[24]

The catalytic activity of BACE1 is tightly regulated by pH, thus the opening of the active site cleft is dependent upon BACE1 localizing to acidic compartments such as endosomes, where APP_{WT} processing primarily takes place.[25,26] As BACE1 trafficks through the secretory pathway, the immature, prodomain containing form of the protein is processed into a mature, more catalytically active form,[27,28] which is subsequently trafficked to the cell surface before re-internalization into endosomes.[29,30] Other than PrP^C only two other proteins have been shown to regulate BACE1 via its prodomain, namely PS1 and SorLA.[20,31] Whereas PS1 aids the maturation and trafficking of BACE1, SorLA regulates the BACE1 processing of APP in a manner similar to PrP^C leading to a decrease in Aβ peptide generation shown in both cell culture models and SorLA knockout mice.[19,20] SorLA mediates its inhibitory effect by retaining BACE1 in the trans Golgi network (TGN) preventing its association with its other interacting partner APP.[20] Interestingly, an unbiased microarray screen for genes differentially expressed in lymphoblasts of patients with sporadic AD revealed that SorLA protein levels were dramatically reduced.[32]

In our recent study in reference 24, we used colocalization with subcellular markers to assess the effect of PrP^C on BACE1 trafficking. This revealed that PrP^C caused retention of BACE1 in the TGN, reducing the trafficking of BACE1 to the cell surface and endosomes where it preferentially cleaves APP_{WT}. We demonstrated that the reduction in BACE1 localization to endosomes only amounted to ~30%,[24] whereas the reduction in APP processing was > 95%.[17] This discrepancy can be explained by the likelihood that only a small pool of total BACE1 protein within cells may be intended for APP processing, as BACE1 has several other substrates which are cleaved in other subcellular compartments. For example, the amyloid precursor like proteins (APLPs) are cleaved within endosomal compartments,[33,34] α-2,6-sialyltransferase (ST6Gal-1) resides in the TGN where it is cleaved by BACE1,[35] and low density lipoprotein receptor-related protein-1 (LRP-1) and BACE1 interact at the cell surface where BACE1 releases C-terminal fragments of LRP1.[36] We hypothesized that PrP^C sequesters BACE1 into membrane subcompartments separate to those which contain APP, and that this separation subsequently leads to changes in the downstream trafficking of BACE1 into endosomal compartments where it cleaves APP_{WT}.[37] A recent study on the regulation of BACE1 internalization demonstrated that BACE1 needs to be sorted from ARF6 positive endosomes to RAB5 positive early endosomes for the proteolytic processing of APP to occur,[21] which suggests that a small change in the cellular localization of BACE1 early in the secretory pathway could hinder this downstream sorting process. Clearly there are several proteins, including PrP^C, which are able to modulate the cellular activity of BACE1, primarily by altering its trafficking to endosomes that contain APP. It may be a combination of cellular factors/stresses that alter one or more of these regulatory proteins that ultimately leads to de-regulation of BACE1 activity and consequently Aβ homeostasis.

In the non-amyloidogenic processing of APP, α-secretases [notably ADAM10 and other members of the A distintegrin and metalloproteinase (ADAM) family] cleave APP in the middle of the Aβ sequence precluding the production of intact Aβ peptides.[5] Overexpression of ADAM10 in transgenic mice resulted in an increase in α-secretase cleavage of APP and a reduction in Aβ production and deposition,[38] reinforcing the consensus view that the amyloidogenic and non-amyloidogenic APP processing pathways are reciprocally regulated. Recently, the shedding of various proteins, including PrP^C, by ADAM10 was investigated in vivo using conditional neuron specific ADAM10 knockout mice.[39,40] As well as confirming ADAM10 to be the PrP^C sheddase,[41] they also observed an increase in PrP^C protein levels and re-location of PrP^C to intracellular compartments of the secretory pathway, namely the endoplasmic reticulum (ER) and Golgi upon deletion of ADAM10.[39] Interestingly, in the earlier study in reference 40, the same authors reported that deletion of ADAM10, as well as reducing significantly the α-secretase cleavage of APP, also somewhat surprisingly led to a reduction in sAPPβ and Aβ, suggesting that somehow altering ADAM10 levels was also impacting on the cleavage of APP by BACE1. From our recent study in reference 24, a potential explanation for why deleting ADAM10 has such an adverse

effect on the cleavage of APP by BACE1 becomes apparent. The accumulation of PrP^C in the secretory pathway of the ADAM10 knockout mice leads to retention of BACE1 in these compartments and subsequent reduction in the processing of APP. In addition to its role in shedding PrP^C, ADAM10 has also been reported to be responsible for its endoproteolytic cleavage to generate the neuroprotective N1 fragment.[42-44] However, the role of ADAM10 in this endoproteolytic cleavage of PrP^C is controversial.[39,41]

To extend our analysis of the effect of PrP^C on BACE1 we examined the effect of PrP^C deletion on Aβ production and deposition in the J20 transgenic mouse model of AD.[24] These mice express human APP with the Swedish (K670N/M671L) and Indiana (V717F) familial mutations ($APP_{Swe,Ind}$).[45] Surprisingly, deletion of PrP^C in this transgenic mouse model had no effect on APP proteolytic processing, Aβ plaque deposition, or levels of soluble Aβ or Aβ oligomers.[24] Consistent with this, others have shown that PrP^C deletion in the $APP_{Swe}/PS1_{\Delta E9}$ and $APP_{Swe}/PS1_{L166P}$ transgenic models failed to alter BACE1 processing of APP, Aβ levels and Aβ deposition,[46,47] and overexpression of PrP^C in $APP_{Swe,Ind}$ transgenic mice resulted in only a minor increase in Aβ plaque formation but no difference in Aβ40 or Aβ42 levels.[48] In addition, a recent study by Cissé et al.[49] showed that PrP^C deletion in the J20 transgenic mice did not change hippocampal levels of Aβ. The common denominator in all of the transgenic animals used in these studies is the Swedish familial mutation in APP. BACE1 is known to cleave APP_{WT} and APP_{Swe} in different subcellular compartments: the cleavage of APP_{Swe} occurs primarily in the TGN,[25,50] whereas the cleavage of APP_{WT} occurs in the endosomes.[30,51,52] As PrP^C interacted with the prodomain containing form of BACE1 increasing its localization to the TGN, while decreasing the amount in endosomes, we considered whether the cleavage of APP_{WT} and APP_{Swe} by BACE1 were differentially affected by PrP^C. Using HEK cells expressing either APP_{WT} or APP_{Swe} we found that although PrP^C inhibited the activity of BACE1 toward APP_{WT} it had no such inhibitory effect on the activity of BACE1 toward APP_{Swe}.[24]

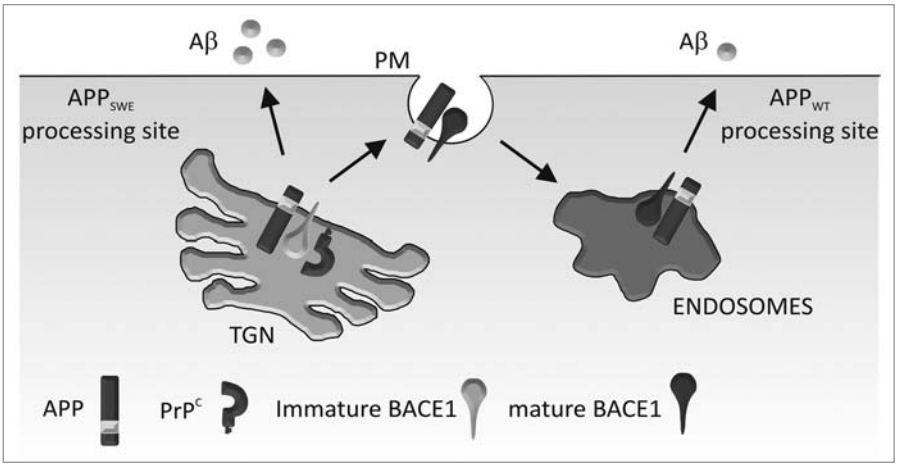

Figure 1. Schematic diagram depicting PrP^C regulation of BACE1 in relation to APP_{WT} and APP_{Swe}. PrP^C interacts with the pro-domain of BACE1 in its immature form in the TGN, slowing its maturation and trafficking to endosomes (via the cell surface). In the TGN, BACE1 preferentially cleaves APP_{Swe}; in the endosomes, it preferentially cleaves APP_{WT}. Our model shows that PrP^C inhibits BACE1 cleavage of APP_{WT}, but not APP_{Swe} which leads to increased Aβ formation. PM, plasma membrane.

Thus the different subcellular sites of action of BACE1 toward APP_{WT} (endosomes) and APP_{Swe} (TGN) would appear to explain the lack of effect of PrP^C deletion on APP processing and Aβ deposition in the $APP_{Swe,Ind}$/PrP null mice (**Fig. 1**).

Of the APP mouse models currently listed on Alzforum (www.alzforum.org/res/com/tra/app/) 76% contain genetic familial mutations, with 57% containing the Swedish mutation and only 2% expressing human APP_{WT}. The transgenic models incorporating familial mutations not only in APP, but also in PS1, PS2 and tau have contributed immensely to the study of AD, however, they all have their limitations and no one model completely encapsulates all aspects of the cellular and behavioral pathology of AD (reviewed in refs. 3, 53 and 54). Our study has highlighted a significant limitation of the transgenic models incorporating the Swedish mutation in APP. Others have recently highlighted that caution is needed when using transgenic animal models with familial AD mutations as the underlying mechanisms driving amyloid accumulation in familial AD and in sporadic AD may well be subtly different.[55] As less than 1% of AD cases are caused by inheritable mutations[3] and with our aging population, there is a great need for a transgenic mouse model of sporadic AD that will facilitate detailed analysis of the disease process occurring in the vast majority of AD patients.

From our studies in cell and animal models we proposed that a normal function of PrP^C was to regulate the production of the neurotoxic Aβ and therefore to protect against AD.[17,18,24] A previous immunohistochemical study showed that there was a decrease in PrP^C in the occipital and frontal gray matter in the brains of sporadic AD patients[56] and PrP^C levels in cerebrospinal fluid were found to decrease with dementia severity in AD.[57] A brief report also showed a decrease of PrP^C in the hippocampus and frontal cortex in AD,[58] however, the number of cases (two AD and three controls) was too small for statistical analysis and the case information presented was insufficient to draw any relevant conclusions about the link between PrP^C expression and AD. Recently, we performed a larger study (with 7 AD cases and 7 age-matched controls) where we found that PrP^C was decreased in the hippocampus and temporal cortex in patients with sporadic AD compared with the age-matched controls,[59] consistent with our proposal that PrP^C could regulate the production of Aβ (**Fig. 2**). In contrast to our data[59] and that of Velayos et al. a more recent study reported that there was no difference in PrP^C levels in the hippocampus, superior frontal cortex (BA9) and superior-middle temporal cortex (BA21–22)

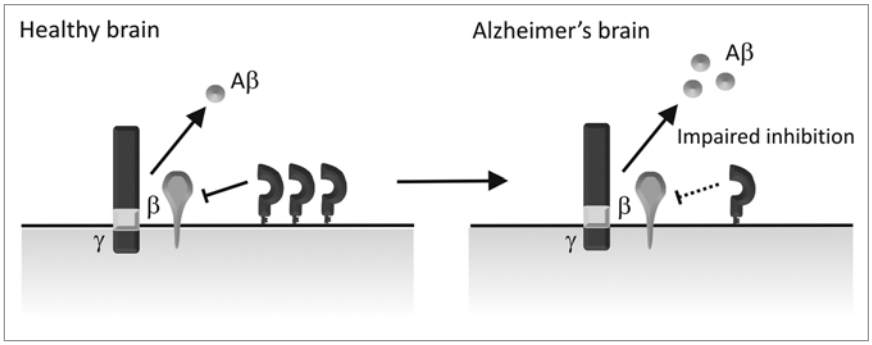

Figure 2. Schematic diagram depicting PrP^C regulation of BACE1 in sporadic AD brains. In the healthy brain, PrP^C interacts with BACE1 inhibiting its cleavage of APP and thereby keeping the level of Aβ in check. In sporadic AD, PrP^C levels are reduced, leading to impaired BACE1 inhibition and increased Aβ formation.

of patients with no cognitive impairment (NCI), amnestic mild cognitive impairment (aMCI), mild AD (mAD) and AD patients.[60] The reasons for the differences between these studies is not immediately apparent, although Saijo et al. did not differentiate between sporadic and familial AD cases in their cohort making direct comparison with our data difficult.

Like many of the biological changes that occur as a consequence of the pathological cascade in AD, this reduction in PrP^C could simply be explained by downstream events associated with neurodegeneration. However, there was no loss of PrP^C in the brains of individuals harboring genetic mutations that cause familial AD,[59] suggesting that reduced expression of PrP^C is not simply an effect of Aβ accumulation and the neurodegeneration in sporadic AD. Thus, this reduction in PrP^C would appear to reflect a primary mechanism of disease and not merely a secondary consequence of other AD-associated changes. Although aging is the greatest risk factor for AD,[4] the cause of the association is unknown. The activity of BACE1 increases with age and this increase may be sufficient over time to alter the balance of Aβ generation and clearance and ultimately plaque deposition.[61] Using an aging series of human brains (ages 20–88), we found that PrP^C decreases with age in areas of the brain affected in AD,[59] possibly providing a molecular mechanism for how the increase of BACE1 activity with age could affect AD progression. PrP^C is known to protect neuronal cells against oxidative stress (reviewed in refs. 10 and 62), possibly in part via generation of the N1 fragment,[63] and aging is associated with an increase in reactive oxygen species, with oxidative stress being an early event in the pathogenesis of AD.[64-66] Therefore, the reduction of PrP^C seen in the aging and sporadic AD brain would likely also contribute to the increased susceptibility of neurons to oxidative stress, exacerbating AD pathology.[59]

PrP^C has also recently been identified as a high affinity receptor for Aβ-oligomers[47,67-69] which are considered to be the neurotoxic species in AD.[70,71] However, there are contradictory results on whether the binding of these oligomers to PrP^C is required to mediate their toxic effects and thus the functional role of the binding interactions is yet to be firmly established.[46,72-74] Although deletion of PrP^C alleviated the memory deficits in the $APP_{Swe}/PS1_{\Delta E9}$ mice,[47] ablation of PrP^C did not ameliorate cognitive dysfunction in the J20 transgenic mice.[49] One possible reason for these discordant results is the inclusion of the PS1 transgene in the former mice which may be having a complicating effect on the interpretation of these data.

In summary, PrP^C has been shown to protect neurons against oxidative stress, as well as to inhibit the β-secretase cleavage of APP_{WT}, thereby reducing Aβ generation, and PrP^C is downregulated in sporadic AD and in aging. In light of these observations, depletion of PrP^C, as suggested by some as a potential treatment for AD, may have significant deleterious effects on the pathogenesis of sporadic AD. Clearly further work is required, including the development of appropriate animal models, to clarify the role of PrP^C in AD.

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